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(54) Title: TOPICAL ADMINISTRATION OF ANGIOTENSIN–CONVERTING ENZYME INHIBITORS

(57) Abstract

Topical ocular compositions comprising an angiotensin–converting enzyme inhibitor and methods for treating the retinopathy, neuropathy, and nephropathy associated with diabetes are disclosed.

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TOPICAL ADMINISTRATION OF ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

The present invention is directed to the topical ocular administration of angiotensin-converting enzyme (ACE) inhibitors for the treatment of diabetic neuropathy and/or nephropathy and diabetic retinopathy.

Background of the Invention

There is extensive literature regarding the use of ACE inhibitors for the treatment of persons suffering from type I diabetes, that is, insulin dependent diabetes mellitus. Taguma, et al., "Effect of captopril on heavy proteinuria in azotemic diabetics," *N. Eng. J. Med.*, **313**, 1617-1620 (1985); Marre, et al., "Converting enzyme and kidney function in normotensive diabetic patients with persistent microalbuminuria," *Br. Med. J.*, **294**, 1448-1452 (1987); Brichard, et al., "Renal function, glycemic control and perindopril in diabetic patients," *Clin. Exp. Theory Pract.*,. **A11** (Suppl 2), 545-554 (1989); Rudberg, et al., "Enalapril reduces microalbuminuria in young normotensive type I (insulin-dependent) diabetic patients irrespective of its hypotensive effect," *Diabetologia*, **33**, 470-476 (1990); Mathiesen, et al., "Efficacy of captoprilin postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria," *BMJ*, **303**, 81-87 (1991); and Wiegmann, et al., "Effect of angiotensin-converting enzyme inhibition on renal function and albuminuria in normotensive type I diabetic patients," *Diabetes*, **41**, 62-67 (1992). The use of these compounds is believed to be involved in preventing the nephropathy associated with type I diabetes.

Further research has indicated the possibility that ACE inhibitors might have a role in treating diabetic retinopathy. In a two year trial with sixteen patients with type I diabetes, early diabetic nephropathy, and normal blood pressures, systemic administration of the ACE inhibitor, captopril, was shown to decrease retinal deterioration. Jackson, et al., "Angtiotensin-converting enzyme inhibitor therapy and diabetic retinopathy," *Ann. Ophth 24*, 99-103 (1992). In a more extensive study, lisinopril (10mg or 20mg) was shown to have beneficial effects on the progression of retinopathy in patients with type I diabetes. Chaturvedi, et al., "The effect of the ACE inhibitor lisinopril on retinopathy in normotensive people with insulin dependent diabetes mellitus - findings from EUCLID, a randomized controlled trial," *The Lancet*, **351**, 28-31 (1997).

ACE inhibitors orally because diabetes is a systemic disease with manifestations throughout the body, e.g., the eyes and kidneys.

Summary of the Invention

The present invention is directed to compositions of ACE inhibitors that can be administered topically to the eye at concentrations to treat ocular manifestations of type I diabetes. Furthermore, if the patient can tolerate effective systemic concentrations of ACE inhibitors, higher concentrations of ACE inhibitors can be administered topically to the eyes, effectively treating not only ocular problems associated with diabetes, but also the neuropathy and/or nephropathy usually occurring in patients with type I diabetes.

Description of Preferred Embodiments

The compositions of the present invention contain pharmaceutically effective amounts of at least one ACE inhibitor, typically 0.01 - 10.0 percent by weight (wt.%). The concentration will vary depending on the potency of the ACE inhibitor and whether it is desirable to dose for treatment mainly of ocular tissues or whether systemic dosing is desired for the treatment of ocular tissues and other sites of damage associated with type I diabetes. The compositions are dosed one to four times per day according to the discretion of a skilled clinician.

ACE inhibitors and ACE inhibitor prodrugs which can be formulated and used according to the present invention include, but are not limited to captopril, lisinopril, perindopril, enalapril, enalaprilat, SQ 29,852, fosinopril, fosinoprilat, zofenopril, zofenoprilat, and ceronapril.

Lisinopril is the preferred ACE inhibitor due to its potency and long half life (greater than twelve hours). Consequently, the concentration at which it is dosed can be lower and its dosing frequency reduced compared to other ACE inhibitors. For treating mainly eye tissues the concentration is about 0.05 to 3.0 wt.%, preferably 0.1 to 1.0 wt.% dosed once or twice a day. For systemic dosing via topical administration, the concentration is about 0.5 to 10.0 wt.%, preferably 1.0 to 3.0 wt.% dosed twice daily.

The following compositions are illustrative; they are not limiting.

Ingredient Description	Concentration			
	Solution	Solution	Suspension	Solution
Active				
Lisinopril	1.0%	3.0%	1.0%	5.0%
Polymer				
Carbopol		0.2%		
Eucheuma*			0.6%	
EHEC**				2.0%
Drug Carrier				
Cyclodextrin		5.0%		5.0%
Duolite AP (Ion Exchange Resin)			1.0%	
Preservative				
BAC	0.01%	0.01%		
Polyquad			0.005%	
Cosmocil				0.005%
Chelator				
Edetate sodium			0.005%	
Tonicity Agent	Q. S. to 300 mOsm	Q. S. to 300 mOsm	Q. S. to 300 mOsm	Q. S. to 300 mOsm
Mannitol		4.0%		
Glycerol			3.0%	
NaCl	0.5%			0.2%
Na_2SO_4				0.8%
Buffer				
NaOAc				0.07%
Na_2HPO_4	0.2%			
Tromethamine /Borate			0.5%	
Acid / Base	Q.S. to pH 6 - 7	Q.S. to pH 6 - 7	Q.S. to pH 6 - 7	Q.S. to pH 6 - 7
HCl	Ö	Ö	Ö	Ö
NaOH	Ö	Ö	Ö	Ö

* U.S. Patent Nos. 5,403,841 and 5,212,162

** (ethylhydroxyalkylcellulose) U.S. Patent No. 5,681,800

We Claim:

1. A composition for topical ocular administration comprising a pharmaceutically effective amount of an angiotensin-converting enzyme inhibitor.

2. The composition of Claim 1 wherein the angiotensin-converting enzyme inhibitor is lisinopril.

3. A method for treating diabetic retinopathy which comprises administering topically to an eye a composition comprising a pharmaceutically effective amount of an angiotensin-converting enzyme inhibitor.

4. The method of Claim 3 wherein the angiotensin-converting enzyme inhibitor is lisinopril.

5. A method for treating the neuropathy, retinopathy, and nephropathy associated with diabetes which comprises administering topically to an eye a composition comprising a pharmaceutically effective amount of an angiotensin-converting enzyme inhibitor.

6. The method of Claim 5 wherein the angiotensin-converting enzyme inhibitor is lisinopril.

INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 98/27183

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/00 A61K31/40 A61K38/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	PATENT ABSTRACTS OF JAPAN vol. 098, no. 013, 30 November 1998 & JP 10 218792 A (SANTEN PHARMACEUT CO LTD), 18 August 1998 see abstract	1,2
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X	EP 0 114 333 A (SCHERING CORP) 1 August 1984 see the whole document	1

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[X] Further documents are listed in the continuation of box C.

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20 May 1999	07/06/1999

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Category °	Citation of document, with indication,where appropnate, of the relevant passages	Relevant to claim No.
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Information on patent family members

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